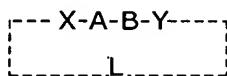


## Claims

## 1. A compound having the general formula I

(I)



5 where the dashed line indicates that formula I is optionally cyclic, and the bonds shown represent covalent bonds;

and wherein A represents a chemical moiety having an amino group (radical) and a carboxy group that forms part of the peptide bond connecting A to X and B;

10 B represents a chemical moiety having an amino group (radical) and a carboxy group that forms part of the peptide bond connecting B to A and Y;

15 X represents a peptide sequence of from 1 to 3 amino acid residues which independently may be an L or D form when Y represents a C-terminal peptide sequence of from 2 to 5 amino acid residues which may independently be L- or D-forms;

20 or X represents an N-terminal modification of the group A-B when Y represents a C-terminal peptide sequence of from 2 to 5 amino acid residues which may independently be L- or D-forms; or

X represents a peptide sequence of from 2 to 5 amino acid residues which may independently be L- or D-forms when Y represents a C-terminal peptide sequence of from 1 to 3 amino acid residues which independently may be an L or D form;

25 and when formula I represents a linear peptide X is optionally chemically modified at its N-terminal,

and L is an optional linking group comprising from 0 to 8 backbone atoms;

30 and a mirror image or a retro analogue of formula I, or a derivative of formula I which is a pharmaceutically acceptable salt, an alkyl, aryl or aralkyl ester, an amide, a mono or disubstituted amide where the substituent is an alkyl, an aryl or an aralkyl, a hydrazide, or an alcohol;

with the proviso that the compounds

35 with the proviso that the compounds

H-Gly-Pro-Leu-Gly-Pro-OH,

H-Pro-4Hyp-Gly-Ala-Gly-OH,

N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-Gly-Ala-Gly-OH,  
N-3-phenylpropionyl-Pro-4Hyp-Gly-Ala-Gly-OH,  
N-3-phenylpropyl-Pro-4Hyp-Gly-Ala-Gly-OH,  
N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-Gly-Ala-OH,  
5 N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-Gly-OH,  
N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-OH,  
N-3-(4-hydroxyphenyl)propionyl-Pro-Pro-Gly-Ala-Gly-OH,  
H-Gly-Ala-Gly-4Hyp-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-4Hyp-Pro-Tyr-OH,  
10 H-Ala-Gly-4Hyp-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Sar-Pro-Gly-Ala-Gly-OH,  
H-Gly-Pro-Sar-Gly-Ala-GlyOH,  
H-Gly-Sar-Sar-Gly-Ala-Gly-OH,  
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-I)-NH<sub>2</sub>,  
15 H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-F)-NH<sub>2</sub>  
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-Cl)-NH<sub>2</sub>  
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-Br)-NH<sub>2</sub>  
H-Arg-Ala-Gly-Hyp-Pro-Tyr-NH<sub>2</sub>  
H-Val-Ala-Gly-Hyp-Pro-Tyr-NH<sub>2</sub>  
20 H-Ala-Ala-Gly-Hyp-Pro-Tyr-NH<sub>2</sub>  
H-Gly-Ala-Gly-Hyp-His-Tyr-NH<sub>2</sub>  
H-Gly-Ala-Gly-Hyp-Pro-Phe-NH<sub>2</sub>  
Cyclo(CF<sub>3</sub>C(OH)-Gly-Ala-Gly-4Hyp-Pro-Tyr-CONH), and  
Cyclo(CO-Gly-Ala-Gly-4Hyp-Pro-Tyr-CONH).  
25 are not covered by the general formula I.

2. A compound according to claim 1 wherein said covalent bonds are selected from peptide bonds, disulphide bonds, ester bonds, reduced amide bonds, alkoxy bonds, oxycarbonyl bonds, and acyloxyalkoxy bonds.

30 3. A compound according to the preceding claim wherein said covalent bond is a peptide bond.

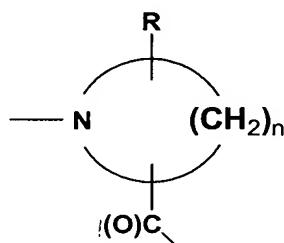
35 4. A compound according to any one of the preceding claims wherein A and B each represents an amino acid or an amino acid derivative having functional amino and carboxy groups.

5. A compound according to any one of claims 1 to 4 wherein A-B represents a dipeptide

selected from the group consisting of Sar-Sar, Sar-Hyp, Hyp-Sar, Pro-Sar, Sar-Pro, Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp, where Pro and Hyp independently may be an L or D form, where the ring structure of Pro and Hyp is optionally substituted with halogen, nitro, methyl, amino, or phenyl, and Hyp represents 3-hydroxyproline or 4-hydroxyproline, or

5 one or both of the amino acid residues of A-B is a Sar, or N-cyclohexylglycine residue.

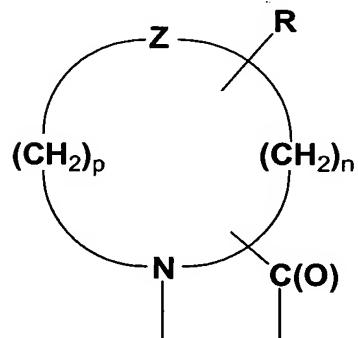
6. A compound according to any one of claims 1 to 3 wherein the groups A and B each independently represents a group of the formula II



(II)

10 wherein n is an integer having the value 3, 4, or 5, and R represents an optional substituent, preferably selected from the group consisting of halogen, phenyl, hydroxy, NH<sub>2</sub>, and C(1-6)alkyl optionally substituted with halogen.

7. A compound according to any one of claims 1 to 3 wherein the groups A and B are  
15 represented by the formula IIa



IIa

Wherein n is an integer having the value 0, 1, 2, and 3, p is an integer having the value 0, 20 1, 2, and 3, Z represents O or S, and R represents an optional substituent, preferably selected from the group consisting of halogen, phenyl, hydroxy, NH<sub>2</sub>, and C(1-6)alkyl.

8. A compound according any one of the two preceding claims wherein R is selected from the group consisting of F, Cl, Br, phenyl, OH, NH<sub>2</sub>, CH<sub>3</sub>, and CF<sub>3</sub>.

9. A compound according to any one of the preceding claims wherein A and B  
5 independently represents an amino acid residue having a saturated carbocyclic structure of 4, 5 or 6 members and where in said carbocyclic structure further comprises one or more heteroatoms.

10. A compound according to the preceding claim wherein said heteroatoms is selected  
10 from the group consisting of N, O and S.

11. A compound according to the preceding claim selected from the group consisting of L and D forms and derivatives of Prolin having one or more substituents in the 3, 4 or 5 position, said substituents being selected from hydroxy, amino and phenyl.

15

12. A compound according to any one of claims 6 and 7 wherein A and B is selected from the group consisting of N- and C(O)- radicals of the following compounds:  
D/L-azetidin-3-carboxylic acid,  
D/L-azetidin-2-carboxylic acid,  
20 D/L-Indolin-2-carboxylic acid,  
D/L-1,3-dihydro-isoindol-1-carboxylic acid,  
D/L-thiazolidin-4-carboxylic acid,  
D/L-pipecolinic acid,  
D/L-Nipecotinic acid,  
25 Isonipecotinic acid,  
L/D-2-carboxymorpholin,  
L/D-1,2,3,4-tetrahydroquinolin-3-carboxylic acid,  
L/D-1,2,3,4-tetrahydroquinolin-3-carboxylic acid, and  
4-carboxy-4-phenyl-piperidin.

30

13. A compound according to any one of the preceding claims wherein formula I represents a linear peptide wherein said chemical modification of the N-terminal of X is an acylation with an optionally substituted straight, branched, saturated, unsaturated, or aromatic C(1-22)carboxylic acid where the substituent is selected from hydroxy, halogen, 35 C(1-6)alkyl, nitro or cyano and may be situated on the carbon chain or the aromatic moiety.

14. A compound according to the preceding claim wherein said C(1-22)carboxylic acid is a C(1-7)carboxylic acid selected from the group consisting of acetic acid; propionic acid, butyric acid and isomers thereof; and benzoic acid.

5 15. A compound according to any one of the preceding claims wherein formula I represents a linear peptide wherein said chemical modification of the N-terminal of X is an alkylation with an optionally substituted C(1-22)alkyl or aryl C(1-22)alkyl where the substituent is selected from hydroxy, halogen, C(1-6)alkyl, nitro or cyano and may be situated on the carbon chain or the aromatic moiety.

10

16. A compound according to the preceding claim wherein said C(1-22)alkyl is a C(1-6)alkyl and said aryl C(1-22)alkyl is an aryl C(1-3)alkyl, respectively.

17. A compound according to the preceding claim wherein said C(1-6)alkyl or a C(7-15)aralkyl is selected from the group consisting of methyl, ethyl, propyl, butyl, phenylpropyl, 2-hydroxyphenylpropyl, and 4-hydroxyphenylpropyl.

18. A compound according to claim 15 wherein X represents one amino acid residue.

20 19. A compound according to the preceding claim wherein said amino acid residue is selected from the group consisting of L-Tyr and D-Tyr optionally acylated with a C(1-4)carboxylic acid when Y represents a C-terminal peptide sequence of from 2 to 5 amino acid residues as defined in claim 1.

25 20. A compound according to the preceding claim wherein said C(1-4)carboxylic acid is acetic acid.

21. A compound according to any one of claims 12 to 20 wherein A-B is selected from the group consisting of Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp where Pro and Hyp 30 independently may be an L or D form.

22. A compound according to the preceding claim wherein Hyp represents L-4Hyp.

23. A compound according to any one of claims 12 to 22 wherein Y represents a peptide of 35 3 or 4 amino acid residues being independently L- or D-forms.

24. A compound according to the preceding claim having Sar or Gly at its C-terminal.

25. A compound according to any one of claims 18 to 27 wherein Y represents a peptide sequence selected from the group consisting of

5 Gly-L-Ala-Gly,  
Gly-L-Ala-Gly,  
Gly-D-Ala-Gly,  
Gly-D-Ala-Gly, and  
Sar-Aib-Sar.

10 26. A compound according to any one of claims 1 to 11 wherein formula I represents a linear peptide and X represents an N-terminal modification of the group A-B.

15 27. A compound according to the preceding claim wherein said modification is an acylation of the N-terminal of A-B with a compound selected from the group consisting of phenylpropionic acid and derivatives thereof; phenylacetic acid and derivatives thereof; phenoxyacetic acid and derivatives thereof; benzoylglycine and derivatives thereof; and phenylglycine and derivatives thereof.

20 28. A compound of formula I selected from the group consisting of  
Ac-L-Tyr-L-Pro-L-4Hyp-Gly-L-Ala-Gly,  
Ac-D-Tyr-D-Pro-D-4Hyp-Gly-D-Ala-Gly,  
A portion of various compounds 4HPPA-L-Pro-L-4Hyp-Gly-L-Ala-Gly, and  
a pharmaceutically acceptable salt, an alkyl ester, an amide, an alkylamide, an aryl amide,  
25 a dialkylamide, an aryl/alkyl amide, a hydrazide, or an alcohol thereof.

29. A compound according to any one of claims 1 to 11 wherein formula I represents a cyclic compound.

30 30. A compound according to the preceding claim wherein said cyclic compound is a cyclic peptide sequence comprising all L-forms, all D-forms, or a sequence of mixed L- and D-forms of the amino acid residues thereof.

35 31. a compound according to the preceding claim wherein A-B is selected from the group consisting of  
Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp where Pro and Hyp independently may be an L or D form and Hyp preferably represents 4-hydroxyproline.

32. a compound according to the preceding claim wherein A-B represents unsubstituted L-Pro-L-4Hyp, L-4Hyp-L-Pro, D-Pro-D-4Hyp, or D-4Hyp-D-Pro.

5 33. A compound according to any one of claims 31 to 34 wherein X represents a single amino acid residue.

34. A compound according to the preceding claim wherein X represents L-Tyr or D-Tyr optionally further substituted with halogen, phenyl, hydroxy, NH<sub>2</sub>, C(1-6)alkoxy, aryloxy,

10 and C(1-6)alkyl optionally substituted with halogen, at its aromatic ring when Y represents a peptide of 3 or 4 amino acid residues being independently L- or D-forms.

35. A compound according to the preceding claim wherein Y has Asp, Asn, Gln or Glu at its C-terminal.

15

37. A compound according to the preceding claim wherein Y represents a peptide sequence selected from the group consisting of

Gly-L-Ala-L-Asn,

Gly-D-Ala-L-Asn,

20 Gly-L-Ala-Gly-L-Asn,

Gly-L-Ala-Gly-D-Asn,

Gly-L-Ala-L-Gln,

Gly-L-Ala-Gly-L-Gln,

Gly-L-Ala-Gly-D-Gln,

25 Gly-D-Ala-D-Asn,

Gly-D-Ala-Gly-D-Asn,

Gly-D-Ala-Gly-L-Asn,

Gly-D-Ala-D-Gln,

Gly-D-Ala-Gly-D-Gln,

30 Gly-D-Ala-L-Gln,

Gly-D-Ala-Gly-D-Gln,

Gly-L-Ala-L-Asp,

Gly-D-Ala-L-Asp,

Gly-L-Ala-Gly-L-Asp,

35 Gly-L-Ala-Gly-D-Asp,

Gly-L-Ala-L-Glu,

Gly-L-Ala-Gly-L-Glu,

Gly-L-Ala-Gly-D-Glu,  
Gly-D-Ala-D-Asp,  
Gly-D-Ala-Gly-D-Asp,  
Gly-D-Ala-Gly-L-Asp,  
5 Gly-D-Ala-D-Glu,  
Gly-D-Ala-Gly-D-Glu,  
Gly-D-Ala-L-Glu,  
Gly-D-Ala-Gly-D-Glu.

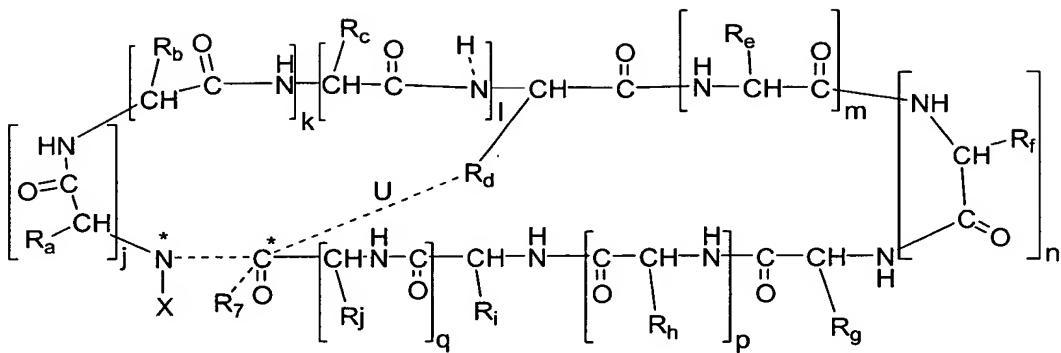
10 38. A compound according to wherein X represents a peptide sequence selected from the group consisting of  
Gly-L-Ala-L-Asp,  
Gly-L-Ala-Gly-L-Asp,  
Gly-L-Ala-L-Glu,  
15 Gly-L-Ala-Gly-L-Glu,  
Gly-D-Ala-D-Asp,  
Gly-D-Ala-Gly-D-Asp,  
Gly-D-Ala-D-Glu,  
Gly-D-Ala-Gly-D-Glu,  
20 and Y represents a single amino acid residue.

39. A compound according to the preceding claim wherein Y represents L-Tyr or D-Tyr optionally further substituted with halogen, phenyl, hydroxy, NH<sub>2</sub>, C(1-6)alkoxy, aryloxy, and C(1-6)alkyl optionally substituted with halogen, at its aromatic ring.

25 40. A compound of formula I where the groups X and Y are connected via a peptide bond or a disulphide bond to form a cyclic compound.

41. A compound of the general formula XII

30 (XII)



representing a peptide sequence wherein the amino acid residues may be D- and/or L-forms, and having the N-terminal at N\* and the C-terminal at C\* and being optionally

5 cyclic via a covalent bond between N\* and C\* as shown by a broken line or between R<sub>d</sub> and C\* as shown by the broken line U; and wherein

X represents an N-terminal moiety such as a photoprobe capable of being bond to the amino terminal N\*, or an acyl group derived from a C(2-22)alkyl carboxylic acid, such as acetic acid, propionic acid, butyric acid and other fatty acids, such as behenic acid,

10 optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, C(1-6)alkyl, nitro and cyano; or X represents hydrogen;

R<sub>7</sub> represents OH, NH<sub>2</sub>, NHHN<sub>2</sub> or OR<sub>8</sub> when the bond between N\* and C\* is missing, or R<sub>7</sub> is absent when there is a bond between N\* and C\*;

R<sub>8</sub> represents H or a straight or branched C(1-6)alkyl group, an aryl or an aralkyl group.

15 R<sub>a</sub> represents the amino acid side chain of Hyp or Pro;

R<sub>b</sub> represents the amino acid side chain of Hyp or Pro;

R<sub>c</sub> represents the amino acid side chain of Gly, Sar, an aromatic amino acid side chain optionally substituted with one or more hydroxy, halogen or lower alkoxy group in the aromatic ring;

20 R<sub>d</sub> represents the amino acid side chain of Ala, Gly, Glu, Asp, Dab, Dapa, Lys, Asn, Gln, Orn, or Cys;

R<sub>e</sub> represents the amino acid side chain of Ala;

R<sub>f</sub> represents the amino acid side chain of Ala, Sar or Gly;

25 R<sub>g</sub> represents any amino acid side chain except the side chain of L-4Hyp or a moiety of formula II or IIa;

R<sub>h</sub> represents the amino acid side chain of Ala, or R<sub>g</sub> represents a moiety of formula II or IIa;

R<sub>i</sub> represents the amino acid side chain of Gly or R<sub>i</sub> represents an aromatic amino acid optionally substituted with one or more halogen groups in the aromatic ring;

30 R<sub>j</sub> represents Asn, Gln, Asp, Glu, Cys or Tyr;

and each of j, k, l, m, n, p and q is independently 0 or 1;  
and the retro form, all D form, or retro all-D form of the peptide sequence of formula XII,  
and  
salts and amides thereof.

5

42. A compound according to the preceding claim wherein X is selected from the group consisting of Ac and the photoprobes ASAL optionally iodinated in position 5 to yield the group 2-hydroxy-4-azido-5-iodo benzoyl, and AB.

10 43. A compound according to any one of the two preceding claims wherein R<sub>7</sub> is NH<sub>2</sub>.

44. A compound according to any one of the three preceding claims wherein R<sub>a</sub> is the amino acid side chain of Pro.

15 45. A compound according to any one of the four preceding claims wherein R<sub>b</sub> is the amino acid side chain of Hyp.

46. A compound according to any one of the five preceding claims wherein R<sub>c</sub> is the amino acid side chain of Gly or Tyr.

20

47. A compound according to any one of the six preceding claims wherein R<sub>d</sub> is selected from the group consisting of the amino acid side chain of Gly, Asp or Glu, Dapa and Dab.

48. A compound according to any one of the seven preceding claims wherein R<sub>f</sub> is Ala or Gly.

25

49. A compound according to any one of the eight preceding claims wherein R<sub>g</sub> is the amino acid side chain of Pro, Asn or Gly.

30 50. A compound according to the preceding claim wherein R<sub>g</sub> is the amino acid side chain of Asn, Gly, D-4Hyp or L-/D-Pro when formula XII represents a linear peptide, or when formula XII represents a peptide cyclised between N\* and C\* then R<sub>g</sub> represents the amino acid side chain of L-/D-4Hyp or L-/D-Pro.

35 51. A compound according to any one of the ten preceding claims wherein R<sub>h</sub> is the amino acid side chain of Ala when U is missing, or R<sub>h</sub> is Pro or Hyp when U is present.

52. A compound according to any one of the eleven preceding claims wherein R<sub>i</sub> is preferably Tyr, Phe, Trp, Nal optionally substituted with one or more hydroxy, F or Cl, in the aromatic ring.

5 53. A compound according to any one of the twelve preceding claims wherein R<sub>j</sub> is selected from the group consisting of the amino acid side chain of Asp, Glu, and Tyr.

54. A linear peptide according to claim 41 of formula XII which is an retro all-D form.

10 55. A peptide compound of formula XII consisting of between 3 and 9 amino acid residues, more preferably between 3 and 7 amino acid residues and wherein j and k are preferably 0 when U is present, j and k are preferably 1 when U is missing and formula XII represents a cyclic peptide, m is preferably 0 when U is missing, p is preferably 1 when U is present, and q is preferably 0 when U is present.

15 56. A compound according to claim 1 or 43 and having the general formula XIII  
(XIII)                    X-(G')<sub>a</sub>-A-G'-(Px)<sub>2</sub>-(Y')<sub>b</sub>-R<sub>7</sub>

20 specifying a peptide sequence wherein the amino acid residues may be L and/or D forms, and  
wherein

X represents H or Ac;

G' represents a glycine residue or a glycine analogue such as Sar;

25 A represents alanine;

Px represents an amino acid residue of formula II or IIa such as Hyp or Pro;

Y' represents tyrosine or phenylalanine optionally substituted in the phenyl ring with halogen or hydroxy;

a and b are independently 0 or 1,

30 R<sub>7</sub> represents OH, NH<sub>2</sub>, NHHN<sub>2</sub>, Asn-NH<sub>2</sub>, or Gln-NH<sub>2</sub>;  
and retro forms thereof and salts thereof.

57. A compound according to the preceding claim wherein X represents Ac and all amino acid residues are L-forms.

35

58. A compound according to any one of the two preceding claims wherein G' is glycine.

59. A compound according to any one of the three preceding claims wherein Px is Pro.

60. A compound according to any one of the four preceding claims wherein Y' is Tyr.

61. A compound according to any one of the five preceding claims wherein R<sub>7</sub> is NH<sub>2</sub>.

5 62. A retro compound of formula XIII having the formula XIIIa: X-(Y')<sub>b</sub>-(Px)<sub>2</sub>-G'-A-(G')<sub>a</sub>-R<sub>7</sub>,  
wherein all amino acid residues are D-forms and wherein all symbols have the same  
meaning as defined above for formula XIII.

10 63. A peptide compound of formula XIII wherein at least one Px residue is a D-amino acid  
and the rest are L-amino acids.

64. A cyclic sequence of formula XIII wherein X represents H, R<sub>7</sub> represents Asn or Gln  
having a covalent bond to Y' which represents Tyr, b is 1, and a is 1.

15 65. A compound of formula 2: H-GAG-(Pa)<sub>2</sub>-NH<sub>2</sub> as defined herein or a salt thereof.

66. A compound according to the preceding claim selected from the group consisting of  
H-Gly-Ala-Gly-D-Hyp-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-D-Pro-Pro-Tyr-NH<sub>2</sub>,

20 H-Gly-Ala-Gly-D-Pro-Ala-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-Gly-D-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-D-Hyp-Ala-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-D-Hyp-D-Pro-Tyr-NH<sub>2</sub>, and pharmaceutically acceptable salts thereof.

25 67. A compound of formula 3: H-GAG-(Px)<sub>2</sub>-Y-NH<sub>2</sub> as defined herein or a salt thereof.

68. A compound according to the preceding claim selected from the group consisting of  
H-Gly-Ala-Gly-NCG-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-T4C-Pro-Tyr-NH<sub>2</sub>,

30 H-Gly-Ala-Gly-A2C-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Gly-PC-Pro-Tyr-NH<sub>2</sub>, and pharmaceutically acceptable salts thereof.

69. A compound of formula 8: H-G'-A-G'-(Px)2-Y-NH<sub>2</sub> as defined herein or a salt thereof.

35 70. A compound according to the preceding claim selected from the group consisting of H-  
Sar-Ala-Sar-Hyp-Pro-Tyr-NH<sub>2</sub>,  
H-Gly-Ala-Sar-Hyp-Pro-Tyr-NH<sub>2</sub>, and pharmaceutically acceptable salts thereof.

71. A compound of formula 6: X-G-D-A-G-(D-Px)<sub>2</sub>-D-Y-NH<sub>2</sub> as defined herein and salts thereof.

5 72. A compound according to the preceding claim selected from the group consisting of H-Gly-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr-NH<sub>2</sub>,  
H-Gly-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr-D-Asp-OH,  
Ac-D-Tyr-D-Pro-D-Hyp-Gly-D-Ala-Gly-NH<sub>2</sub>,  
Ac-D-Tyr(3,5-di-I)-D-Pro-D-Hyp-Gly-D-Ala-Gly-NH<sub>2</sub>,

10 Ac-D-Tyr(phenyl ring mono-iodo substituted)-D-Pro-D-Hyp-Gly-D-Ala-Gly-NH<sub>2</sub>,  
Ac-D-Tyr-D-Pro-D-Hyp-(12,13C,15N-Gly)-D-Ala-(1,213C,15N-Gly)-NH<sub>2</sub>, and  
pharmaceutically acceptable salts thereof.

73. A compound of formula 9: X-(Y)p-(Px)<sub>2</sub>-GAG-NH<sub>2</sub> as defined herein and salts thereof.

15 74. A compound according to the preceding claim selected from the group consisting of ASAL-Pro-Hyp-Gly-Ala-Gly-NH<sub>2</sub>,  
ASAL(mono-iodo substituted)-Pro-Hyp-Gly-Ala-Gly-NH<sub>2</sub>,  
AB-Tyr-Pro-Hyp-Gly-Ala-Gly-NH<sub>2</sub>,

20 AB-Tyr(3,5-di-I)-Pro-Hyp-Gly-Ala-Gly-NH<sub>2</sub>, and pharmaceutically acceptable salts thereof.

75. A compound of formula 10: Cyclo(-GAG-(Px)<sub>2</sub>-Y-N/Q-) as defined herein and salts thereof.

76. A compound according to the preceding claim selected from the group consisting of cyclo(-Gly-Ala-Gly-Hyp-Pro-Tyr-Gln-),

25 cyclo(-Gly-Ala-Gly-Hyp-Pro-Tyr-Asn-),  
cyclo(-Gly-Ala-Gly-Pro-Pro-Tyr-Asn-), and pharmaceutically acceptable salts thereof.

77. A compound of formula 11: Cyclo(-Y-(Px)<sub>2</sub>-GA-(G)<sub>q</sub>-N/Q-) as defined herein and salts thereof.

30 78. A compound according to the preceding claim selected from the group consisting of Compound 3 cyclo(-Tyr-Pro-Hyp-Gly-Ala-Gly-Asn-),  
Compound 4 cyclo(-Tyr-Pro-Hyp-Gly-Ala-Asn-),  
cyclo(-Tyr(3-I, 5-I)-Pro-4Hyp-Gly-Ala-Gly-Asn), and pharmaceutically acceptable salts  
35 thereof.

79. A compound of formula 12: X-Zd-G(N/Q)Y-NH<sub>2</sub> as defined herein and salts thereof.

80. A compound according to the preceding claim selected from the group consisting of

H-Gly-Ala-Gly-Asn-Tyr-NH<sub>2</sub>,

Ac-Gly-Asn-Tyr-NH<sub>2</sub>,

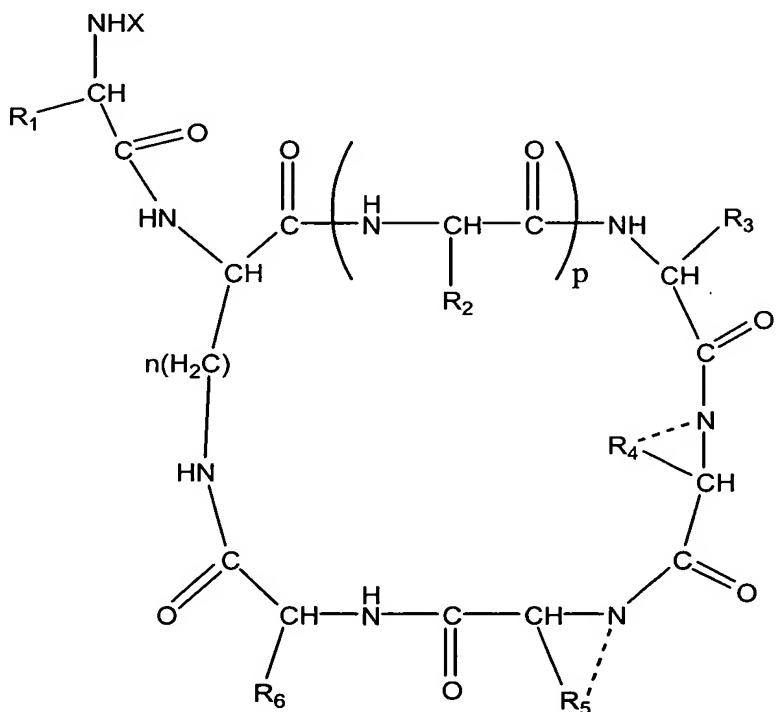
5 H-Gly-Asn-Tyr-NH<sub>2</sub>,

Ac-Ala-Gly-Asn-Tyr-NH<sub>2</sub>,

H-Ala-Gly-Asn-Tyr-NH<sub>2</sub>, and pharmaceutically acceptable salts thereof.

81. A cyclic peptide compound of formula XII further characterised in having the general

10 formulae XIV:



**XIV**

wherein

X represents H or an N-terminal moiety such as a photoprobe capable of binding to the N

15 terminal or an acylation with a C(2-22)alkyl carboxylic acid, such as acetic acid, propionic acid, butyric acid and other fatty acids such as behenic acid, being optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, C(1-6)alkyl, nitro and cyano;

R<sub>1</sub> represents H or CH<sub>3</sub>;

20 R<sub>2</sub> and R<sub>3</sub> are different or the same and represent any possible amino acid side chain;

—·— represents an optional bond;

$R_5$  and  $R_4$  represent any possible amino acid side chain or when the optional bond is present  $R_5$  and  $R_4$  represent together with the attached C and N atoms a proline ring which is optionally substituted with OH, preferably in the 4-position, or  $R_5$  and  $R_4$  represent together with the attached C and N atoms a moiety of formula II or IIa above;

5  $R_6$  represents an aromatic amino acid side chain optionally substituted in the aromatic ring with one or more substituents selected from halogen, nitro and hydroxy;  
 $p$  is 0 or 1;  
 $n$  is 1, 2, 3 or 4;  
and salts thereof.

10

82. A compound according to the preceding claim wherein X represents H or the photoprobe groups AB or ASAL which is optionally iodinated as described herein.

15 83. A compound according to any one of the two preceding claims wherein  $R_1$  represents

H.

84. A compound according to any one of the three preceding claims wherein  $R_2$  and  $R_3$  are different or the same and represent H or  $CH_3$ .

20 85. A compound according to any one of the four preceding claims wherein  $R_5$  and  $R_4$  represent together with the attached C and N atoms Pro or Hyp.

86. A compound according to any one of the five preceding claims wherein  $R_6$  represents Tyr.

25

87. A compound according to any one of the six preceding claims wherein  $p$  is 1.

88. A compound according to any one of the seven preceding claims wherein  $n$  is 1.

30 89. A compound of formula XIV selected from the group consisting of

35 H-Gly-Dapa-Gly-Hyp-Pro-Tyr

H-Gly-Dab-Gly-Hyp-Pro-Tyr

H-Gly-Dab-Ala-Gly-Hyp-Pro-Tyr

5

H-Gly-Dapa-Ala-Gly-Hyp-Pro-Tyr

10

H-Gly-D-Dapa-Gly-D-Hyp-D-Pro-D-Tyr

H-Gly-D-Dab-Gly-D-Hyp-D-Pro-D-Tyr

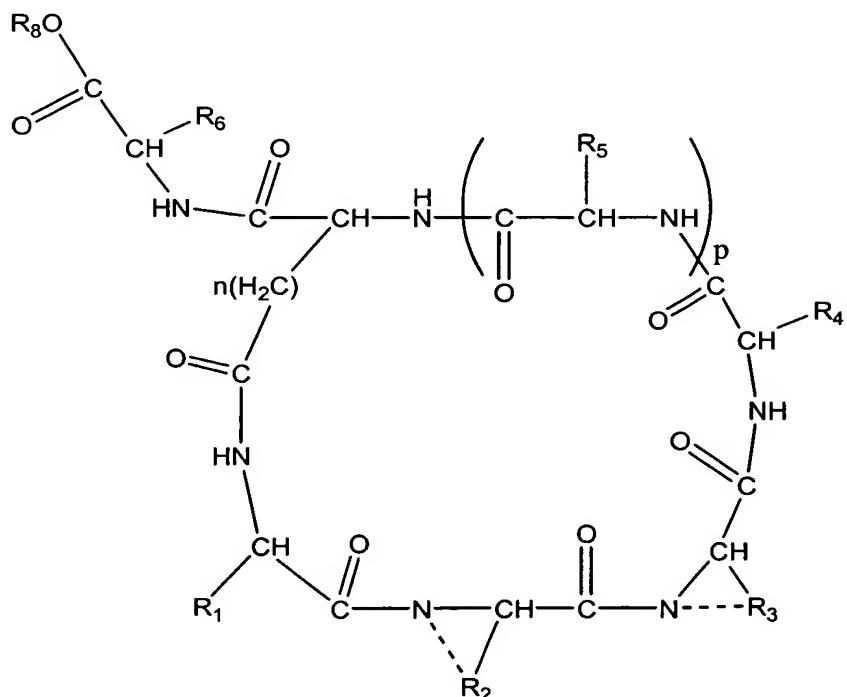
H-Gly-D-Dab-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr

15 H-Gly-D-Dapa-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr

and pharmaceutically acceptable salts thereof.

90. A compound of formula XII further characterised by the general formula XV

20

**XV**Wherein R<sub>8</sub> represents H or a C(1-6)alkyl group;

R<sub>6</sub> represents H or CH<sub>3</sub>;

R<sub>4</sub> and R<sub>5</sub> are different or the same and represent any possible amino acid side chain;

----- represents an optional bond;

R<sub>2</sub> and R<sub>3</sub> represent any possible amino acid side chain, or when the optional bond is

5 present R<sub>2</sub> and R<sub>3</sub> represent together with the attached C and N atoms a proline ring which is optionally substituted with OH preferably in the 4-position or R<sub>2</sub> and R<sub>3</sub> represent a moiety of formula II or IIa;

R<sub>1</sub> represents an aromatic amino acid side chain;

p is 0 or 1;

10 n is 1, 2, 3 or 4;

and salts thereof.

91. A compound according to the preceding claims wherein R<sub>8</sub> represents H.

15 92. A compound according to any one of the two preceding claims wherein R<sub>4</sub> and R<sub>5</sub> are different or the same and represent the amino acid side chain of Gly or Ala.

93. A compound according to any one of the three preceding claims wherein R<sub>2</sub> and R<sub>3</sub> represent together with the attached C and N atoms Pro or Hyp.

20

94. A compound according to any one of the four preceding claims wherein R<sub>1</sub> represents Tyr.

95. A compound according to any one of the five preceding claims wherein p is 1.

25

96. A compound according to any one of the six preceding claims wherein n is 1.

97. A compound of formula XV selected from the group consisting of

30

Tyr-Pro-Hyp-Gly-Glu-Gly-NH<sub>2</sub>

Tyr-Pro-Hyp-Gly-Asp-Gly-NH<sub>2</sub>

35

— Tyr-Pro-Hyp-Gly-Ala-Asp-Gly-NH<sub>2</sub>

|

Tyr-Pro-Hyp-Gly-Ala-Glu-Gly-NH<sub>2</sub>

5  D-Tyr-D-Pro-D-Hyp-Gly-D-Glu-Gly-NH<sub>2</sub>

D-Tyr-D-Pro-D-Hyp-Gly-D-Asp-Gly-NH<sub>2</sub>

10  D-Tyr-D-Pro-D-Hyp-Gly-D-Ala-D-Asp-Gly-NH<sub>2</sub>

D-Tyr-D-Pro-D-Hyp-Gly-D-Ala-D-Glu-Gly-NH<sub>2</sub>

ad pharmaceutically acceptable salts thereof.

15 98. A peptide compound wherein the amino acid residues may be L- and/or D-forms, and having the general formula XVI

XVI                    R<sub>1</sub>-Aa<sub>1</sub>-Al-Aa<sub>2</sub>-Ar-R<sub>2</sub>

20 Wherein R<sub>1</sub> represents an optional amide bond between the N and the C terminal of the peptide, H or Ac;

Aa<sub>1</sub> represents a peptide sequence of between 0 and 4 amino acid residues;

Al represents an amino acid residue selected from the group consisting of Gly, beta Alanine and Sar;

25 Aa<sub>2</sub> represents an amino acid residue selected from the group consisting of Asn, Gln, Gly, Tyr, or a chemical unit, such as a hydroxy acid, an amino sulphonic acid, a phosphate group or a hydrocarbon chain connecting G and Ar via 4 covalent bonds;

Ar represents an aromatic amino acid residue, such as a Tyr, Trp, Phe, His, or Nal, optionally substituted with one or more substituents selected from the group consisting of

30 halogen, such as F, Cl, Br, or I, OH, NO<sub>2</sub>, NH<sub>2</sub>, COOH, and CONH;

R<sub>2</sub> represents OH, NH<sub>2</sub> or is missing;

and retro analogues, retro all-D analogues (retro-inverse analogues) and salts thereof.

99. A compound according to the preceding claim wherein Aa<sub>1</sub> is selected from the group consisting of Ala, Gly-Ala, Gly-Asn-Tyr, and Gly-Asn-Tyr-Ala a portion of various listed compounds.

100. A compound according to any one of the two preceding claims wherein A1 represents Gly or Sar.

101. A compound according to any one of the three preceding claims wherein Aa<sub>2</sub>  
5 represents Asn or Gln.

102. A compound according to any one of the four preceding claims wherein Ar represents  
Tyr or Phe optionally substituted with one or more halogen, such as I.

10 103. A compound according to any one of the five preceding claims wherein R<sub>2</sub> represents  
NH<sub>2</sub> when the compound is non-cyclic or R<sub>2</sub> is missing when the compound is cyclic.

104. A compound of formula XVI selected from the group consisting of

H-Gly-Ala-Gly-Asn-Tyr-NH<sub>2</sub>,

15 cyclo(-Tyr-Ala-Ser-Ala-Gly-Asn-),

cyclo(-Tyr-Ala-Ser-Ala-Gly-Asn-),

cyclo(-Tyr-Gly-Asn-Tyr-Ala-Gly-Asn-),

cyclo(-Tyr-Val-Ser-Gly-Ala-Gly-Asn-),

Ac-Gly-Asn-Tyr-NH<sub>2</sub>,

20 H-Gly-Asn-Tyr-NH<sub>2</sub>,

Ac-Ala-Gly-Asn-Tyr-NH<sub>2</sub>,

H-Ala-Gly-Asn-Tyr-NH<sub>2</sub>, and pharmaceutically acceptable salts thereof.

105. A photo labile derivative of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI  
25 herein, characterised in having covalently bound to the N-terminal N atom a photo probe  
selected from the group consisting of azido, diazo compounds including diazirines and  
thiadiazoles, optionally substituted nitrophenyl, and optionally substituted benzophenones.

106. A compound according to the preceding claim selected from the group consisting of  
30 Compound 31, 32, 33, 34 and salts thereof.

107. A thermo labile derivative of a compound of formula I, XII, XIII, XIIIa, XIV, XV or  
XVI herein, characterised in having covalently bound to the N-terminal N atom a thermo  
probe selected from the group consisting of maleimido, optionally substituted pyridyl  
35 disulphides, optionally substituted aliphatic halides, isothiocyanates and isocyanates,  
carbodiimides, activated esters, such as N-hydroxysuccinimide.

108. A compound according to the preceding claim which is  $\text{BrCH}_2\text{CO-Gly-Asn-Tyr-NH}_2$  and salts thereof.

109. A compound according to any one of the preceding claims which shows 5 antiarrhythmic effect in the Langendorf model described herein when used in a concentration of from of  $10^{-13}$  to  $10^{-7}$  M, or preferably in a concentration range of  $10^{-12}$  to  $10^{-9}$  M when diluted in medium.

110. A pharmaceutical composition comprising a compound of formulae I, XII, XIII, XIIIa, 10 XIV, XV and XVI and formulae 2-12 or according to any one of the preceding claims, and a pharmaceutically acceptable carrier or diluent.

111. A composition according to the preceding claim which is an enteric tablet.

15 112. A composition according to claim 110 which is an injection preparation.

113. A method of increasing the gap junctional intercellular communication of mammalian 20 cells subjected to glucose and/or oxygen deprivation comprising administering an effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 to said cells.

114. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2- 12 or according to any one of claims 1-109 for the preparation of a medicament.

25 115. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for the treatment of arrhythmia.

116. Use according to the preceding claim where said arrhythmia is a reentry arrhythmia 30 of either atrial or ventricular origin, including repolarisation alternans arrhythmia where both supraventricular and ventricular tachyarrhythmias may present as tachycardia, flutter or fibrillation.

117. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2- 35 12 or according to any one of claims 1-109 for the preparation of a medicament for prevention and/or treatment of slowed conduction in the heart.

118. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for improval of contractility of the heart.

5 119. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for treatment of diaease states associated with impaired GJIC during metabolic stress, including glucose and oxygen deprivation.

10 120. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for antithrombotic treatment.

15 121. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of osteoporosis.

122. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of joint diseases including arthritis.

20 123. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment disease in poorly vascularized cartilage and joints including arthritis.

25 124. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of joint diseases including arthritis

30 125. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment preventing bone loss and increase the healing of bone fractures.

35 126. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment vascularization of the cornea in disease states with poor nutrition of the cornea and increase the healing of corneal lesions

127. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in treatment of wounds and in particular ischemic ulcers.

5 128. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in the treatment of gastric and duodenal ulcers.

10 129. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 that increase gap junctional coupling and/or GJIC in the vascular wall for the preparation of a medicament for the prevention and/or treatment of hypertension.

15 130. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of medicaments useful in preventing ischemic damage in the brain and for the treatment of organic psychoses that may present with symptoms, such as depression, anxiety, learning and memory deficit, fobias, or hallucinations.

20 131. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in prevention and /or treatment of cataract.

25 132. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in prevention and /or treatment of deafness associated with impaired GJIC.

30 133. Use of a compound formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of gastrointestinal motility disorders.

35 134. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in the treatment of female infertility that is due to poor cell-to-cell coupling in the ovaries.

135. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful along with oxytocin for the induction and facilitation of labour.

136. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in treatment of male infertility associated with impaired cell-to-cell coupling.

5 137. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in improving glucose tolerance in a subject with non-insulin dependent diabetes mellitus due to impaired GJIC between  $\beta$ -cells.

10 138. A method of treatment of arrhythmia comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109.

15 139. A method of treatment according to the preceding claim wherein said arrhythmia is a reentry arrhythmia of either atrial or ventricular origin, including repolarisation alternans arrhythmia where both supraventricular and ventricular tachyarrhythmias may present as tachycardia, flutter or fibrillation comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

20 140. A method of antithrombotic treatment comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

25 141. A method of treatment of osteoporosis comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

30 142. A method of treating or preventing bone loss and increase the healing of bone fractures comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

35 143. A method of treatment of joint diseases including arthritis comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

144. A method of treatment of cancer in tissue of endodermal, mesodermal or ectodermal origin, including carcinomas and hepatocellular and cholangiocellular neoplasms and bone cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

5

145. A method of treatment wounds and in particular ischemic ulcers comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

10

146. A method of treatment gastric and duodenal ulcers comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

15

147. A method of treating or preventing hypertension by increasing gap junctional coupling and/or GJIC in the vascular wall comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

20

148. A method of preventing ischemic damage in the brain and treating organic psychoses that may present with symptoms such as depression, anxiety, learning and memory deficit, fobias, or hallucinations comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

25

149. A method of treating or preventing cataract comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

30

150. A method of treatment of deafness associated with impaired GJIC comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

35

151. A method of treatment of gastrointestinal motility disorders comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

5

152. A method of treatment of female infertility that is due to poor cell-to-cell coupling in the ovaries comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

10

153. A method of induction of and facilitation of labour comprising administering along with oxytocin to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

15

154. A method of treatment of male infertility associated with impaired cell-to-cell coupling comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

20

155. A method of improving glucose tolerance in a subject with non-insulin dependent diabetes mellitus due to impaired GJIC between  $\beta$ -cells comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

25

156. A method of treating or preventing disease in poorly vascularized cartilage and joints comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

30

157. A method according to the preceding claim wherein said disease is arthritis.

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158. A method of treating or preventing cataract comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

159. A method of treating or preventing vascularization of the cornea in disease states with poor nutrition of the cornea and increase the healing of corneal lesions comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of 5 claims 1-109.

160. A method of treating or preventing growth and spreading of cancer cells comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of 10 claims 1-109.

161. A method of treatment of glucose and oxygen deprivation of cells, a tissue, or an organ in a patient suffering therefrom comprising administering to said patient an effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to 15 any one of claims 1-109.

162. A method according to the preceding claim wherein said organ is the heart.